DISCOVERY

Safeguarding Neurons After Stroke

Novel drug therapy prevents destruction of salvageable neurons

BY KAT HENDRIX

Currently, tissue plasminogen activator (tPA), a so-called clot buster drug, is the only pharmacological stroke intervention available. It must be administered within 4.5 hours after the stroke and cannot be given to patients who take blood-thinning drugs due to their elevated bleeding risk. However, recent discoveries by a team of MUSC investigators led by **Stephen Tomlinson, Ph.D.**, professor and vice chair for research and faculty development in MUSC's Department of Microbiology and Immunology, may soon expand post-stroke treatment options.

The team's findings, published online May 16 by *Science Translational Medicine* (doi: 10.1126/scitranslmed.aao6459), describe a novel pharmacological agent that links an antibody fragment, which is capable of recognizing specific cell damage markers appearing after an ischemic stroke, to a complement inhibitor. The therapy, called B4Crry, masks damaged but living neurons—preventing their removal and allowing them time to regain functionality.

"There's an ischemic core where the greatest oxygen deprivation occurs. Neurons in that area are irreparably damaged and die," Tomlinson explains. "But damaged neurons outside the stroke core can be salvaged. Unfortunately, complement becomes activated and signals that these damaged neurons should be cleared from the brain before they get a chance to recover."

The complement system is a component of both the innate and adaptive immune responses, but its dual roles in injury and recovery (neurodegenerative and neuroregenerative processes) make it a challenging target for potential stroke therapies. Tomlinson's team found that live but stressed neurons display danger-associated molecular patterns that trigger complement C3d deposition on the outer cell membrane, tagging the neuron for rapid clearance by inflammatory microglia. "B4Crry also breaks the inflammatory response cycle and prevents chronic inflammation, which we know can continue for many years after a stroke," adds **Ali Alawieh**, an M.D./Ph.D. candidate in the Department of Microbiology and Immunology and first author on the article.

In a murine model of ischemic stroke, animals treated post-stroke with B4Crry showed reduced C3d deposition in the brain, fewer neurological deficits and reduced infarct volume compared to control animals. Over the course of a 15-day recovery period, B4Crry-treated animals also had greater recovery of initial deficits than controls. Overall, the B4Crry-treated group had faster learning curves, better learned memory retention and a four-fold increase in cortical and hippocampal neuroblasts than untreated animals. Importantly, these benefits were evident in animals treated up to 24 hours post-stroke—a markedly longer treatment window than for tPA. Also, unlike tPA, B4Crry in theory could be administered to patients who are at risk for bleeding, once its safety and efficacy have been verified in human clinical trials. Another critical advantage of B4Crry treatment is that, because it is targeted to the site of injury in the brain, it does not increase risk for infections such as pneumonia.

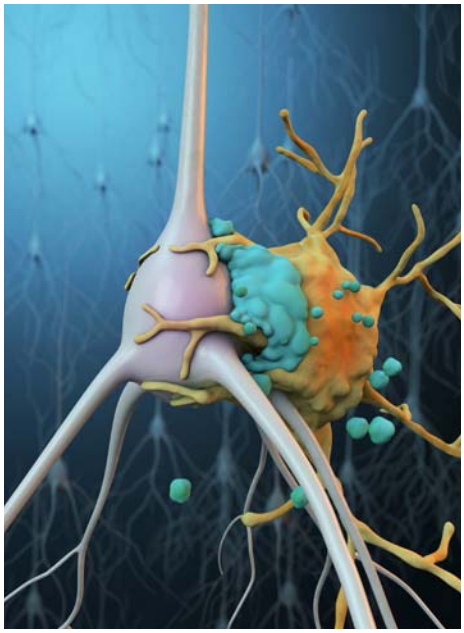

ILLUSTRATION: EMMA VOUGHT

A microglial cell (yellow) attached to an ischemic neuron (gray) that has been tagged by complement proteins (blue)

The team has shown that the B4 epitope is expressed on other injured human tissues and has begun to apply the approach to cardiovascular disease research. Future plans include studying how complement-dependent mechanisms affect outcomes in traumatic brain injury and taking B4Crry therapy into human clinical trials.

Disclosure: Tomlinson is an inventor on a patent application for natural antibody targeted complement inhibitors filed by the University of Colorado and is a consultant for and holds stock from AdMIRx, Inc., a company developing complement inhibitors.

Watch a video interview with Ali Alawieh about this research on the Neurosciences page of the MUSC Health Medical Video Center (MUSChealth.org/medical-video).